REMARKS

Claims 1-4 are pending in this application.

Applicants understand from a telephone call with the Examiner on February 3, 2011, that the Reply After Final with attachments filed January 18, 2011 ("Reply After Final"), was considered but not entered into the record. Applicants incorporate by reference herein the Reply After Final, and address the Office's comments in the Advisory Action below.

Rejection under 35 U.S.C. § 112, First Paragraph

The Office maintains the rejection of claims 3 and 4 under 35 U.S.C. § 112, first paragraph, as allegedly not enabled. Final Office Action at page 2; Advisory Action at page 2. According to the Office, a "disorder of ischemia such as myocardial infarct is irreversible cell death result[ing] from ischemia which is not treatable by angiogenesis." Final Office Action at page 2. Applicants respectfully contend that, even if the Office's definition were correct, which Applicants do not necessarily agree that it is, this does not render impossible therapy for myocardial infarction.

Claim 3 recites that the "pharmaceutical composition is a therapeutic drug for . . . various diseases caused by ischemia." Claim 4 lists "myocardial infarction" as one possible disease "caused by ischemia." Thus, these claims contemplate a therapy for diseases caused by ischemia. In myocardial infarction, not all of the myocardium in the ischemic area suffers irreversible necrosis. As Gowda teaches, myocardial infarction can "result in regional myocardial dysfunction beyond the borders of infarction [where] usually stunned myocardium lies adjacent to infarcted myocardium." Gowda, R.M. et al., "Reversible Myocardial Dysfunction: Basics and Evaluation," *Int. J. Cardiol.* (2004) vol. 97, pp. 349-353, at 350 ("Gowda"), submitted in the IDS filed herewith. Gowda

further teaches that "[l]arge areas of non-functional but viable myocardium with reversible dysfunction are commonly seen in patients with acute myocardial infarction." *Id.* at Abstract. Similarly, Sasayama explains that "coronary collateral circulation is an alternative source of blood supply to the myocardium jeopardized by failure of the original vessel to provide adequate [blood] flow . . . ," and that

> [a] number of studies suggest that among patients with acute myocardial infarction and unsuccessful intracoronary thrombolytic therapy early after onset of symptoms, subsequent improvement in global function and wall motion in the infarct zone frequently can be expected where residual flow was maintained by extensive collaterals to the region perfused by the infarct-related vessel.

Sasayama, S. et al., "Recent Insights Into Coronary Collateral Circulation," *J. Am. Heart Assoc.* (1992) vol. 85, p. 1197-1204, at 1197 ("Sasayama"), submitted in the IDS filed herewith. These cites demonstrate that in the case of myocardial infarction or other ischemic event in the heart, there are cells in the heart that survive despite the infarction or the ischemic event. If this were not the case, the "person" recited in claim 1 would be dead. A "therapeutic drug" as recited in claim 3, therefore, seeks to improve the condition of the cells in the heart that survived an ischemic event, or more specifically an infarction. Indeed, the aim of therapeutic angiogenesis for ischemic heart disease is to promote self-protective angiogenesis exogenously and alleviate myocardial ischemia, thereby avoiding heart failure by saving more myocardial cells and preventing myocardial remodeling. *See* Freedman, S. B. et al., "Therapeutic Angiogenesis for Ischemic Cardiovascular Disease," *J. Mol. Cell Cardiol.* (2001) vol. 33, pp. 379-393 ("Freedman"), submitted in the IDS filed herewith.

The Office now asserts that the references discussed in the Reply After Final are "limited to angiogenic growth in 'reversible' dysfunctional tissue [and] explicitly on

'impaired myocardial dysfunction' of post-ischemic event[s], see Gowda et al. p. 350 left col. description for 'viable myocites.'" Advisory Action at page 2. According to the Office, those references "support[] that angiogenic agent can improve dysfunctional ischemic tissue not dead tissue i.e. ischemic heart disease, ischemic brain disease not myocardial infarct or cerebral infarct." *Id.* The Office's statements on this point demonstrate that at least claim 3, reciting a "therapeutic drug for . . . diseases caused by ischemia" is enabled.

Regarding myocardial infarction, Applicants agree with the Office to the extent that dead tissue cannot be revived. As explained above, a therapeutic drug for myocardial infarction provides therapy by improving the condition of cells in the heart that survived the infarct. However, Applicants continue to disagree with this rejection in that the irreversible death of *individual cells* should be distinguished from the health of the *entire organ* as affected by a myocardial infarction. Applicants note that independent claim 1 recites "[a] method for promoting angiogenesis," and a person of ordinary skill in the art would understand that such a method relates to the treatment of living rather than dead tissue.

The Office now provides two references in the Advisory Action: an excerpt from the Cecil Textbook of Medicine that purportedly "clearly defines" the term infarction "to describe irreversible cellular injury and necrosis occurring as a consequence of prolonged ischemia," and an internet posting from Wikipedia "providing a definition of brain ischemia including cerebral infarction." Advisory Action at page 2 (citations omitted). Applicants address those two references below.

The Cecil Textbook of Medicine, page 247 cited by the Office, appears to teach that "[m]yocardial infarction is the term used to describe irreversible cellular injury and

necrosis occurring as a consequence of prolonged ischemia." Nothing in that description contradicts Applicants' discussion above that a therapeutic drug improves the condition of heart cells that survive a myocardial infarction. With respect to the Wikipedia posting also cited by the Office, that information is not prior art against the instant application, as it was "last modified on January 28, 2011." Wikipedia posting at page 22. In any event, the Wikipedia posting appears to teach that "[i]n an ischemic stroke, blood supply to part of the brain is decreased, leading to dysfunction of the brain tissue in that area." *Id.* at page 3. That information indeed contemplates survival of brain cells after an ischemic event. Likewise, as discussed above for myocardial infarction, some brain cells do survive the infarct event, otherwise the person would be dead. In the context of cerebral infarction, a therapeutic drug targets those cells that survived in the brain post-infarction.

Applicants respectfully remind the Office that "the pending claims must be given their broadest reasonable interpretation consistent with the specification." M.P.E.P. § 2111 (quotation omitted). The present specification provides that "[a]ngiogenesis is a process for formation of a systemic vascular network initiating from embryonic stage, and is related to generation via complex processes including not only proliferation of vascular endothelial cells but also migration of endothelial cells or tube formation, formation of basement membrane, etc." Specification at page 1. Further, "by utilizing [growth factors for promoting angiogenesis] and genes thereof, therapeutic methods for the diseases essentially requiring improvement of blood circulation, such as arteriosclerosis obliterans, ischemic heart disease, and the like, have been attempted and examined." *Id.* at 2. Accordingly, in view of the teachings in the specification and knowledge in the art, a person of ordinary skill in the art would recognize that the

"therapeutic drug" of claim 3 provides therapy for "diseases caused by ischemia" such as myocardial infarction and cerebral infarction, as recited in claim 4, by promoting angiogenesis to improve the condition of surviving cells of the affected organ.

At least for the foregoing reasons, Applicants submit that claims 3 and 4 are fully enabled and request that the Office withdraw this rejection.

Rejection under 35 U.S.C. § 103

The Office maintains the rejection of claims 1-4 under 35 U.S.C. § 103(a) as allegedly obvious over U.S. Patent No. 5,656,642 ("Fujioka") in view of Orito et al. (*J. Pharmacol. Exper. Ther.*, 1999) ("Orito"), Da Silva-Azevedo et al. (*Biochem. Biophys. Res. Comm.*, 2002) ("Silva-Azevedo"), and Zhou et al. (*Cell Tissue Res.*, 1998) ("Zhou") supplemented with Sumi et al. (*Biomed. Pharmacother.*, 2007) ("Sumi"). Final Office Action at page 2; Advisory Action at page 2. Applicants continue to respectfully disagree and traverse this rejection.

In the Advisory Action, the Office explains that the "Sumi reference merely provided evidence flow with the inherent property known for the 'class' of compounds disclosed by Fujioka '642." Advisory Action at page 2. Regardless of the alleged reason for relying on Sumi in support of this obviousness rejection, the fact remains that Sumi does not represent the state of knowledge in the art at the time of invention. Moreover, the Office's statement that "a compound cannot be separated from its inherent property" is not applicable to whether method claims 1-4 would have been obvious. Advisory Action at page 2 (emphasis in original). Indeed, as Applicants explained, a later discovered property cannot make that property obvious retroactively back to the time of the invention. *See* M.P.E.P. § 2141.02 ("Obviousness cannot be predicated on what is not known at the time an invention is made, even if the inherency of a certain feature is

later established," *citing In re Rijckaert*, 9 F.2d 1531, 28 U.S.P.Q.2d 1955 (Fed. Cir. 1993)). Consistent with this premise, 35 U.S.C. § 103(a) instructs that obviousness is predicated on whether a claim's "subject matter as a whole would have been obvious *at the time the invention was made* to a person having ordinary skill in the art." Thus, obviousness is predicated on what was known at the time of the invention. Using information disclosed after the time of the invention to support an obviousness rejection is therefore improper.

Seemingly disregarding what a person of ordinary skill in the art would have known *at the time of the invention*, the Office continues to rely on alleged "factual evidence" obtained by combining Sumi with Fujioka. Advisory Action at page 2. The Office asserts that "a compound cannot be separated from its inherent property, thus, it was inherent utility for the claimed compound since the vasodilators of [Fujioka] also have angiogenic propert[ies]." *Id.* The Office continues to improperly deduce obviousness from information known only after the filing date of the present application, i.e., Sumi. Moreover, the present claims recite "[a] method for promoting angiogenesis" by administering a compound of formula (1). As M.P.E.P. § 2112.02 instructs, "[t]he discovery of a new use for an old structure based on unknown properties of the structure might be patentable to the discoverer as a process of using."

The Office refers to Fujioka for allegedly teaching "the claimed compound" for treating disorders that require vasodilation. Final Office Action at page 2. The Office then turns to Orito, Silva-Azevedo, and Zhou to allegedly show that generally, "other vasodilator[s] such as prazosin function analogously on the blood vessel," and that generally "[v]asodilators such as prazosin not only caused vasodilation but also simultaneously affect the tissue to induce angiogenesis." *Id.* at 3. The Office appears to

assume that all compounds like prazosin would induce angiogenesis because they are vasodilators. Indeed, the Office explains that its alleged basis for this rejection is "per ponderous of evidence indicate[s] that [an] adrenergic blocker which has vasodilating activity also result[s] in the downstream angiogenesis (Orito, Azevedo or Zhou)." *Id.; see also* Office Action dated December 4, 2009, at pages 3-4.

In their previous reply, Applicants noted that the Office's assumption is not correct. Some adrenergic blockers (e.g., terazosin and doxazosin) with the same quinazoline structure as prazosin, inhibit angiogenesis. Specifically, the α1 adrenergic blocker prazosin is associated with shear stress-induced angiogenesis. *See* Zhou at 293; Silva-Azevedo at Abstract. On the other hand, studies show that α1-adrenergic blockers terazosin and doxazosin, which have the same quinazoline structure as prazosin, exhibit vasodilating action but *inhibit angiogenesis*. *See, e.g.*, Pan at 724; Keledjian at 1150, both submitted in the IDS filed herewith. In view of this action, researchers have investigated terazosin and doxazosin for potential therapeutic significance in prostate cancer. *Id.* Thus, contrary to the Office's assertion that "it is the innate nature of such compounds to simultaneously hav[e] the [e]ffect of inducing angiogenesis" (Office Action dated December 4, 2009, at page 4), α1-adrenergic blockers having vasodilating action and a quinazoline structure similar to prazosin do not always enhance angiogenic action, and if anything, can *inhibit* angiogenesis. Given this unpredictability in function, one cannot extrapolate back to Fujioka's compound and conclude that it too would function to induce angiogenesis.

Further, the compound recited in independent claim 1 is an antagonist to the α2-adrenergic receptor. The α2-adrenergic receptor differs from the α1-adrenergic receptor

in vascular selectivity and distribution. Given this additional difference, one of ordinary skill in the art could not have concluded that the compound recited in claim 1 would have had angiogenic properties based on the art cited by the Office. *Arguendo*, even if this difference did not exist, as explained above the art does not support the premise that an α1-adrenergic blocker having vasolidator action always enhances angiogenic action. Once all of the teachings in the prior art are properly considered together in their entireties, it becomes evident that a person of ordinary skill in the art would not have had sufficient guidance to have contemplated, let alone to have achieved, the invention of claims 1-4.

In the Advisory Action, the Office now asserts that "[t]he instant scope of compounds is more limited [than Fujioka] (compare claim 1 to instant claim 1). Therefore, the 103(a) rejection is a species/genus relationship." Advisory Action at page 2. Applicants disagree. First, Applicants do not necessarily agree with the Office's statement as to the "instant scope of compounds." Second, Fujioka claims "[a] piperidine compound or an acid addition salt thereof" (Fujioka at claim 1) whereas Applicants claim "[a] method of promoting angiogensis" (present claim 1). A species/genus relationship is not present between Fujioka's claim 1 and instant claim 1. Nothing in Fujioka suggests that the compounds disclosed promote angiogenesis. And, as discussed above, the unpredictability in the art demonstrates the non-obviousness of claims 1-4.

The Office further asserts that "[if] applicants are arguing that the instant smaller genus is unobvious because only this subgenus has angiogenic property not the whole vasodilating genus as the prior art, then, factual evidence supporting such allegation should be presented." Advisory Action at page 2. Applicants are not making that

argument. Applicants' arguments addressed the Office's alleged "basis" for this obviousness rejection, demonstrating how the Office's assumption regarding the nature of vasodilators such as prazosin is incorrect. As Applicants explained, other compounds with a similar structure to prazosin actually inhibit angiogenesis. Nothing in Fujioka suggests that any of the compounds disclosed therein promote angiogenesis. Thus, because the Office's rationale is not supported by the cited art, the Office has not met its initial burden of establishing a *prima facie* case of obviousness. Applicants bear no burden to provide "factual evidence supporting unexpectancy" as the Office requests. Final Office Action at page 3. The burden does not shift to Applicants unless and until the Office establishes a *prima facie* case of obviousness. M.P.E.P. § 2141(IV). The Office has not done so here.

For at least the foregoing reasons, claims 1-4 would not have been obvious in light of the combination of Fujioka, Orito, Da Silva-Azevedo, Zhou, and Sumi. Applicants respectfully request that the Office withdraw this rejection.

Rejection for Obviousness-Type Double Patenting

The Office maintains the rejection of claims 1-4 on the ground of nonstatutory obviousness-type double patenting as allegedly unpatentable over claims 1-18 of Fujioka in view of Orito, Silva-Azevedo, and Zhou supplemented with Sumi, "the same basis" as articulated above for the rejection under 35 U.S.C. § 103(a). Advisory Action at page 2. For the reasons set forth above with regard to obviousness, Applicants submit that the Office has not established a case of *prima facie* obviousness to support this rejection of claims 1-4 based on obviousness-type double patenting. Applicants therefore respectfully request that this rejection be withdrawn.

Conclusion

In view of the foregoing remarks, Applicants respectfully request reconsideration and reexamination of this application, and the timely allowance of claims 1-4.

Please grant any extensions of time required to enter this response and charge any additional required fees to Deposit Account No. 06-0916.

Respectfully submitted,

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